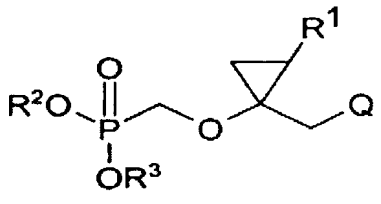
CLAIMS

1. (+)-Trans-isomers of (1-phosphonomethoxy-2-alkylcyclopropyl)methyl nucleoside derivatives represented by the following formula (1):



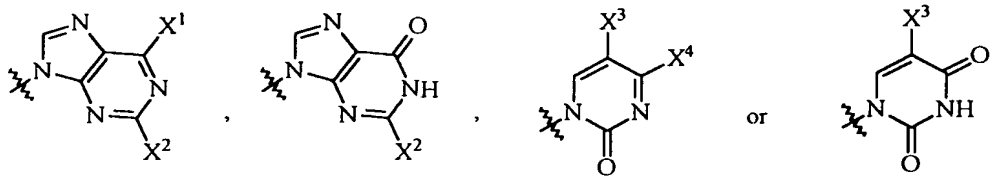
(1)

wherein,

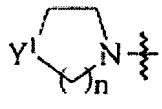
R^1 represents C_1-C_7 alkyl,

R^2 and R^3 independently of one another represent hydrogen, or represent C_1-C_4-alkyl optionally substituted by one or more substituents selected from a group consisting of halogen, C_1-C_4-alkoxy, phenoxy, C_7-C_{10}-phenylalkoxy, and C_2-C_5-acyloxy, or represent C_2-C_7-acyl, C_6-C_{12}-aryl, C_1-C_7-alkylaminocarbonyl, di(C_1-C_7-alkyl)aminocarbonyl or C_3-C_6-cycloalkylaminocarbonyl, or represent -(CH_2)m-OC(=O)-R^4 wherein m denotes an integer of 1 to 12 and R^4 represents C_1-C_{12}-alkyl, C_2-C_7-alkenyl, C_1-C_5-alkoxy, C_1-C_7-alkylamino, di(C_1-C_7-alkyl)amino, C_3-C_6-cycloalkyl, or 3- to 6-membered heterocycle having 1 or 2 hetero atoms selected from a group consisting of nitrogen and oxygen,

Q represents a group having the following formulae:



wherein,

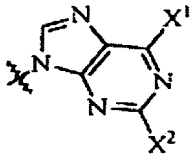
X^1, X^2, X^3 and X^4 independently of one another represent hydrogen, amino, hydroxy, or halogen, or represent C_1-C_7-alkyl, C_1-C_5-alkoxy, allyl, hydroxy-C_1-C_7-alkyl, phenyl, or phenoxy, each of which is optionally substituted by nitro or C_1-C_5-alkoxy, or represent C_6-C_{10}-arylthio which is optionally substituted by nitro, amino, C_1-C_6-alkyl, or C_1-C_4-alkoxy, or represent C_6-C_{12}-arylamino, C_1-C_7-alkylamino, di(C_1-C_7-alkyl)amino, C_3-C_6-cycloalkylamino, or a structure of  wherein n denotes an integer of 1 or 2 and Y^1 represents O, CH_2, or N-R (R represents C_1-C_7-alkyl or C_6-C_{12}-aryl), pharmaceutically acceptable salts, hydrates or solvates thereof.

2. The compounds of claim 1 wherein the pharmaceutically acceptable salt is salt with sulfuric acid, methanesulfonic acid or hydrohalic acid.

3. The compounds of claim 1 wherein

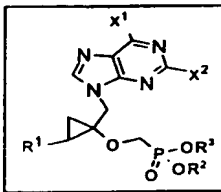
R^1 represents C_1-C_3 alkyl,

R^2 and R^3 independently of one another represent hydrogen, or represent C_1-C_4-alkyl optionally substituted by one or more substituents selected from a group consisting of fluorine, C_1-C_4-alkoxy, and phenoxy, or represent -(CH_2)m-OC(=O)-R^4 wherein m denotes an integer of 1 to 12, and R^4 represents C_1-C_5-alkyl or C_1-C_5-alkoxy,

Q represents  wherein, X^1 represents hydrogen, hydroxy, amino or 4-methoxyphenylthio, or 4-nitrophenylthio, and X^2 represents hydrogen or amino.

4. The compounds of claim 1 which are selected from the group consisting of the compounds described in the following Tables 1a and 1b:

Table 1a



(+)-trans-optical isomer(enantiomer)

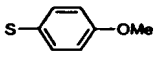
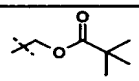
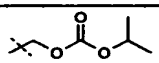
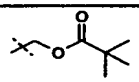
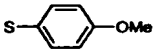
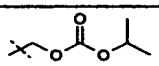
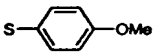
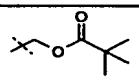
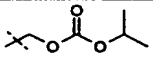
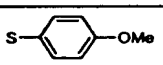
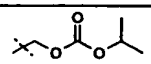
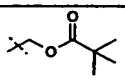
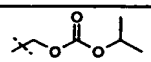
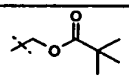
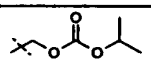
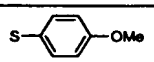
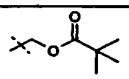
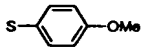
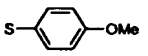
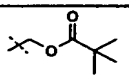
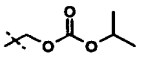
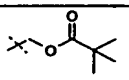
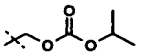
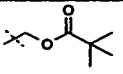
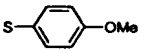
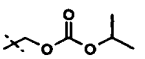
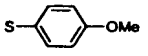
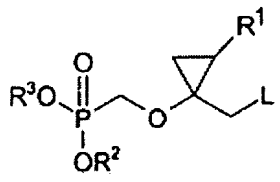
COM. NO.	R^1	R^2 & R^3	X^1	X^2
1	CH_3	H	OH	NH_2
2	CH_3	H	H	NH_2
3	CH_3	H	NH_2	H
4	CH_3	H		NH_2
5	CH_3	H	Cl	NH_2
6	CH_3		H	NH_2
7	CH_3		H	NH_2
8	CH_3			NH_2
9	CH_3			NH_2
10	CH_3		NH_2	H
11	CH_3		NH_2	H
12	C_2H_5	H	OH	NH_2
13	C_2H_5	H	H	NH_2
14	C_2H_5	H	NH_2	H
15	C_2H_5	H		NH_2

Table 1b

16	C_2H_5	H	Cl	NH_2
17	C_2H_5		H	NH_2
18	C_2H_5		H	NH_2
19	C_2H_5		NH_2	H
20	C_2H_5		NH_2	H
21	C_2H_5			NH_2
22	C_2H_5			NH_2
23	C_3H_7	H	OH	NH_2
24	C_3H_7	H	H	NH_2
25	C_3H_7	H	Cl	NH_2
26	C_3H_7	H	NH_2	H
27	C_3H_7	H		NH_2
28	C_3H_7		H	NH_2
29	C_3H_7		H	NH_2
30	C_3H_7		NH_2	H
31	C_3H_7		NH_2	H
32	C_3H_7			H
33	C_3H_7			H
34	CH_3	iso-propyl	Cl	NH_2
35	C_2H_5	iso-propyl	Cl	NH_2

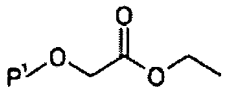
5. A process for preparing a compound represented by the following formula (2):



(2)

in which R^1, R^2 and R^3 are defined as in claim 1, and L represents methanesulfonyloxy, p-toluenesulfonyloxy, or halogen, characterized in that

(a) an ethylglycolate, the alcohol group of which is protected, as represented by the following formula (6):



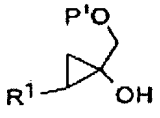
(6)

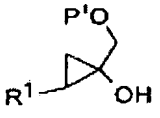
in which P^1 represents an alcohol-protecting group selected from a group consisting of benzyl(Bn), tetrahydropiranyl(THP), t-butydiphenylsilyl(TBDPS) and t-butyldimethylsilyl(TBDMS), is reacted with alkyl magnesium halide represented by the following formula (7):

R^7-MgX (7)

in which R^7 represents C_3-C_7 alkyl and X represents halogen, in the presence of titanium tetraisopropoxide[$Ti(OiPr)_4$],

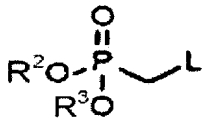
(b) the resulting two cyclopropanol diastereoisomers represented by the following formulae (8) and (9):


(±)-trans-isomer (8)

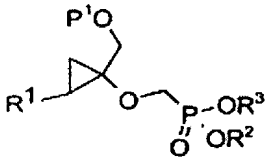

(±)-cis-isomer (9)

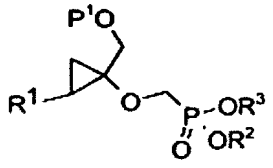
in which R^1 is defined as in claim 1 and P^1 is defined as previously described, are resolved with a silica gel column,

(c) each compound resolved in the step (b) is subjected to an ether-forming reaction with a compound represented by the following formula (10):


(10)

in which R^2 and R^3 are defined as in claim 1, and L is defined as in claim 5, in the presence of base to produce a phosphonate compound represented by the following formula (11) or (12):

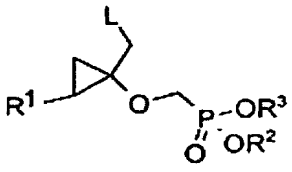

(±)-trans-isomer (11)



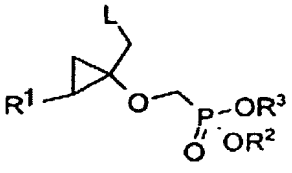
(±)-cis-isomer (12)

in which R^1, R^2 and R^3 are defined as in claim 1, and P^1 is defined as previously described, and

(d) an alcohol-protecting group of the resulting compound of formula (11) or (12) is removed and a leaving group (L) is introduced to produce a compound represented by the following formula (2a) or (2b):



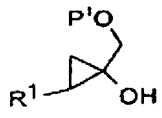
(±)-trans-isomer (2a)



(±)-cis-isomer (2b)

in which R^1, R^2 and R^3 are defined as in claim 1, and L is defined as previously described.

6. A compound represented by the following formula (8):

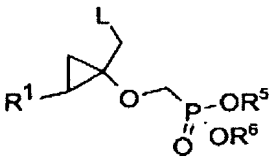


(±)-trans-isomer (8)

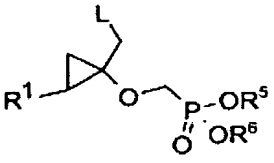
in which R^1 is defined as in claim 1, and P^1 is defined as in claim 5, and

stereoisomers thereof.

7. A process for preparing stereoisomer of the compound of formula (1) as defined in claim 1 characterized in that a compound represented by the following formula (4a) or (4b):



(±)-trans-isomer (4a)



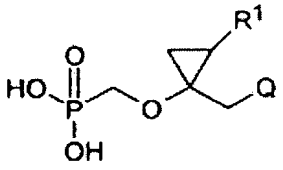
(±)-cis-isomer (4b)

in which R^1 is defined as in claim 1, L is defined as in claim 5, and R^5 and R^6 independently of one another represent C_1-C_7-alkyl, is reacted with a compound represented by the following formula (3):

QH (3)

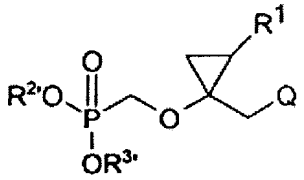
in which Q is defined as in claim 1, and each compound thus obtained is resolved with a chiral column or chiral reagents to produce (+), (-) two optical isomers, each of which is present as an enantiomer enriched isomer, and then each of them is treated with

trimethylsilylbromide(TMSBr) to produce the corresponding (+), (-) two optical isomers of a compound represented by the following formula (1a):



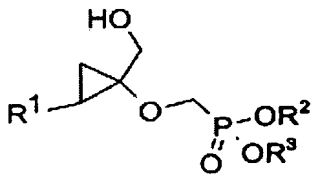
(1a)

in which R^1 and Q are defined as in claim 1, and if necessary, groups $R^{2'}$ and $R^{3'}$ are introduced into the compound thus obtained to produce the corresponding optical isomers of a compound represented by the following formula (1b):

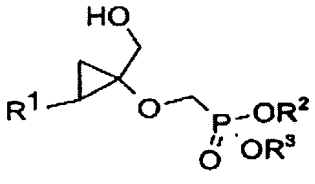


in which R^1 and Q are defined as in claim 1, and $R^{2'}$ and $R^{3'}$ represent R^2 and R^3 with the exception of hydrogen, respectively.

8. A process for preparing stereoisomer of the compound of formula (1) as defined in claim 1 characterized in that a compound represented by the following formula (13) or (14):

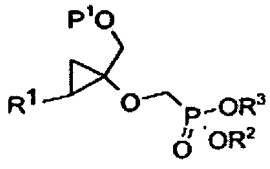


(±)-trans-isomer (13)

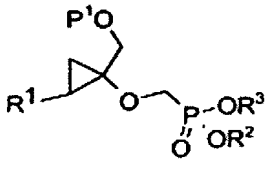


(±)-cis-isomer (14)

in which R^1, R^2 and R^3 are defined as in claim 1, that is obtained by removing an alcohol-protecting group in a compound represented by the following formula (11) or (12):

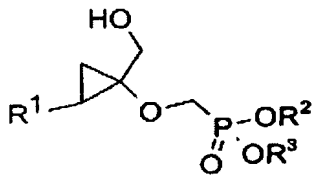


(±)-trans-isomer (11)

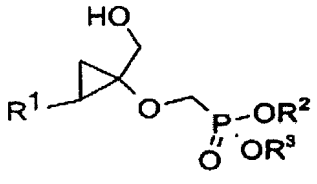


(±)-cis-isomer (12)

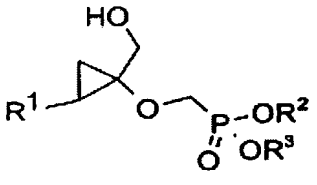
in which R^1, R^2 and R^3 are defined as in claim 1, and P^1 is defined as in claim 5, is resolved with a hydrolase (lipase) to produce enantiomer enriched compounds represented by the following formulae (13a) and (13b) or (14a) or (14b):



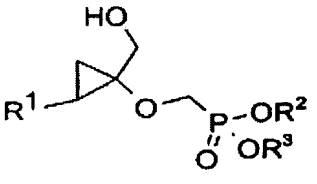
(+)-trans-isomer (13a)



(-)-trans-isomer (13b)

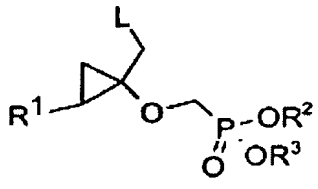


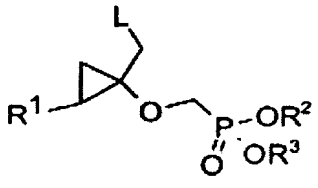
(+)-cis-isomer (14a)

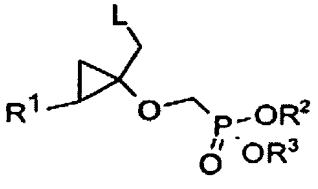


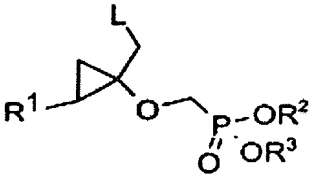
(-)-cis-isomer (14b)

in which R^1, R^2 and R^3 are defined as in claim 1, and further an alcohol group in the compound of formula (13a), (13b), (14a) or (14b) thus obtained is replaced with a leaving group (L) to produce a compound represented by the formula (2aa), (2ab), (2ba) or (2bb):


(+)-trans-isomer (2aa)


(-)-trans-isomer (2ab)


(+)-cis-isomer (2ba)


(-)-cis-isomer (2bb)

in which R^1, R^2 and R^3 are defined as in claim 1, and L is defined as in claim 5, and the resulting compound is reacted with a compound represented by the formula (3):

QH (3)

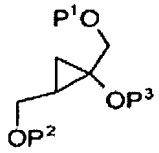
in which Q is defined as in claim 1, to produce the enantiomer enriched compound of formula (1).

9. A process for preparing stereoisomer of the compound of formula (1) as defined in claim 1 characterized in that

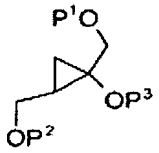
aa) an alcohol-protecting group (P^2) is introduced into (+)-(methylenecyclopropyl)carbinol or (-)-(methylenecyclopropyl)carbinol, whose absolute configuration is known,

bb) the resulting compound is subjected to dihydroxylation reaction,

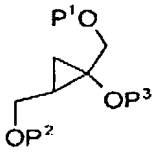
cc) an alcohol-protecting group (P^1) is introduced into the primary hydroxy group in the compound obtained in the above bb) step and an alcohol-protecting group (P^3) is introduced into the tertiary hydroxy group to produce a compound represented by the formula (15a), (15b), (16a) or (16b):



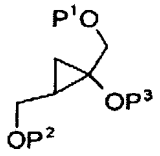
(+)-trans-isomer (15a)



(-)-trans-isomer (15b)



(+)-cis-isomer (16a)

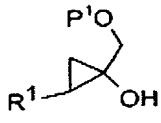


(-)-cis-isomer (16b)

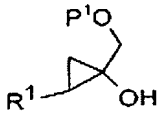
in which P^1 is defined as in claim 7, P^2 represents benzyl, benzoyl, 4-methoxybenzyl, methyloxybenzyl, methyloxymethyl or trityl and P^3 represents 1-methoxyacetyl, acetyl or 2-(trimethylsilyl)-1-ethanesulfony,

dd) the protecting group (P^2) in the resulting compound is removed selectively, the leaving group (L) is introduced, and the compound thus obtained is subjected to a reduction reaction or substituted with C_1-C_7-alkyl group,

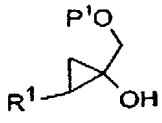
ee) the protecting group (P^3) in the compound thus obtained in the above dd) step is removed to produce a compound represented by the following formula (8a), (8b), (9a) or (9b):

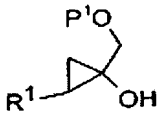


(+)-trans-isomer (8a)



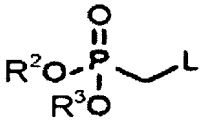
(-)-trans-isomer (8b)


(+)-cis-isomer (9a)

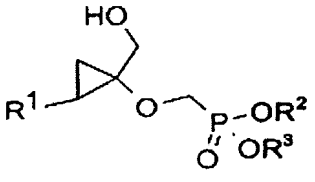

(-)-cis-isomer (9b)

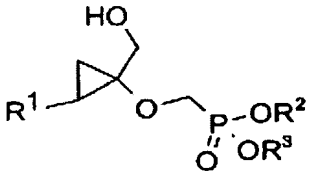
in which R^1 is defined as in claim 1, and P^1 is defined as in claim 5,

ff) the resulting compound in the above step ee) is reacted with a phosphonate compound represented by the following formula (10):

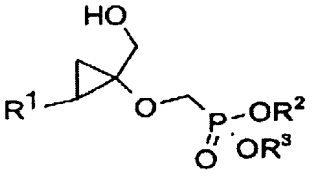

(10)

in which R^2 and R^3 are defined as in claim 1, and L is defined as in claim 5, and the protecting group (P^1) of the compound thus obtained is removed to produce a compound represented by the following formula (13a), (13b), (14a) or (14b):

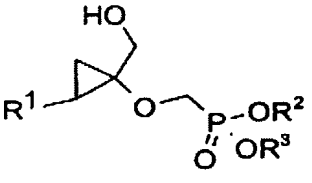

(+)-trans-isomer (13a)



(-)-trans-isomer (13b)



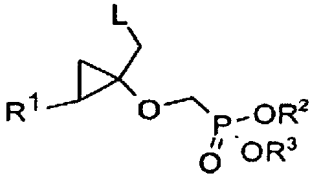
(+)-cis-isomer (14a)



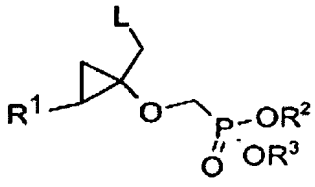
(-)-cis-isomer (14b)

in which R^1, R^2 and R^3 are defined as in claim 1,

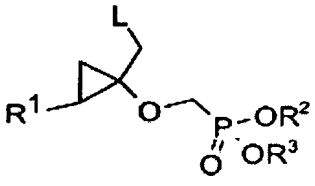
gg) an alcohol group of the resulting compound is replaced with the leaving group (L) to produce a compound represented by the following formula (2aa), (2ab), (2ba) or (2bb):



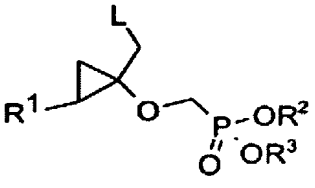
(+)-trans-isomer (2aa)



(-)-trans-isomer (2ab)



(+)-cis-isomer (2ba)



(-)-cis-isomer (2bb)

in which R^1, R^2 and R^3 are defined as in claim 1, and L is defined as in claim 5, and

hh) the resulting compound is reacted with a compound represented by the following formula (3):

QH (3)

in which Q is defined as in claim 1, to produce the enantiomer enriched compound of formula (1).

10. A composition for the treatment of viral diseases, which comprises as an active ingredient (+)-trans-isomer of (1-phosphonomethoxy-2-alkylcyclopropyl)methyl nucleoside derivative of formula (1) as defined in claim 1, pharmaceutically acceptable salt, hydrate, or solvate thereof together with the pharmaceutically acceptable carrier.

11. A composition for the treatment of hepatitis B, which comprises as an active ingredient (+)-trans-isomer of (1-phosphonomethoxy-2-alkylcyclopropyl)methyl nucleoside derivative of formula (1) as defined in claim 1, pharmaceutically acceptable salt, hydrate, or solvate thereof together with the pharmaceutically acceptable carrier.